EXHIBIT 21

February 12, 2001

Comments of the Biotechnology Industry Organization

Re: Recombinant DNA Research,

Proposed Actions Under the NIH Guidelines

65 Fed. Reg. 77655 (December 12, 2000)

Biotechnology Industry Organization

1625 K St., N.W.

Suite 1100

Washington, D.C. 20006

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The Biotechnology Industry Organization (BIO) submits these comments on the proposal published by the National Institutes of Health (NIH) in 65 Fed. Reg. 77655 (December 12, 2000), to revise the "NIH Guidelines for Research Involving Recombinant DNA Molecules" (NIH Guidelines or Guidelines) by making modifications to the provisions governing adverse event reports and annual reports during human gene transfer clinical trials.

EXECUTIVE SUMMARY

The NIH Guidelines apply to any human gene therapy experiment conducted at an institution receiving NIH funding for recombinant DNA research, or conducted by an entity collaborating with such an institution. The Guidelines require the submission to NIH of detailed information about proposed and ongoing clinical trials of gene therapy products, and provide for disclosure of much of this information to the public. In addition, Appendix M to the Guidelines provides that an investigator conducting such a trial must report any serious adverse event immediately to the NIH Office of Biotechnology Activities (OBA). An investigator must also file annual reports with OBA.

On December 12, 2000, NIH proposed revisions to the Guidelines. NIH proposes to define "serious adverse events" as events that are unexpected and possibly associated with the product. These events would be reported to NIH at the same time as they are reported to the Food and Drug Administration (FDA). NIH also proposes to define the content of annual reports, and bases the proposed content on section 312.33 of FDA's regulations, which governs annual reports on investigational drug and biologic products. These reports would be filed at NIH sixty days after the anniversary of the clinical trial start date. Investigators would not be permitted to include individually identifiable information in serious adverse event reports. NIH would not treat any serious adverse event report or annual report as "confidential commercial information" or "trade secret." These reports would be available to the public. Finally, NIH would establish a working group of government and non-government employees, which would review and analyze reports submitted to OBA, and report aggregated trend data to the NIH Recombinant DNA Advisory Committee and the public.

As explained in these comments, the Food and Drug Administration (FDA) has statutory authority to regulate gene therapy products, including clinical trials of some products. Pursuant to this authority it collects detailed information about investigational products and clinical trials, and it reviews both adverse event reports and annual reports during the course of the trials. FDA requirements are embodied in regulations adopted pursuant to explicit statutory authority to prescribe rules governing the clinical trials of new drugs. Those regulations have been adopted in accordance with the Administrative Procedure Act and other statutes and executive orders governing regulatory agencies. By contrast, NIH is by statute a research agency. Indeed, it is the world's premiere biomedical research institute, with an annual budget of over $20 billion, the majority of which is disbursed in grants for extramural research. For over twenty years NIH has – through

conditions attached to these grants – imposed requirements on researchers experimenting with recombinant DNA technology. These conditions have gradually evolved into an elaborate system of oversight that in many ways duplicate or competes with FDA regulation.

The current proposal represents the culmination of this evolution at NIH. These comments explain that the current proposal is both ill-advised and unlawful. *First*, the proposed Guidelines would publicly disclose confidential commercial information and trade secrets, in violation of the Trade Secrets Act and the Takings Clause. *Second*, review and analysis of raw adverse event reports and annual reports by a working group of government employees – but not the working group that NIH proposes – would adequately further NIH's stated goals, while providing the necessary protections for trade secrets and confidential commercial information. *Third*, NIH should allow investigators to submit the same information in serious adverse event reports to NIH as they submit to FDA. *Fourth*, NIH should not model its annual report provision on FDA's annual report regulation. Annual reports to FDA contain highly confidential preliminary safety and effectiveness data whose consideration and release are beyond NIH's stated mission. Also, annual reports to NIH should be filed at the same time as annual reports to FDA.

INTRODUCTION

Nearly two decades have passed since the first human gene transfer experiment. Biotechnology and pharmaceutical companies are researching, developing, and testing hundreds of potential new gene therapy products, for the treatment of disease. Hundreds of gene therapy trials are underway today, as government and private industry work together to find ways for this technology to reach its potential.

Recent reports indicate that the hope for gene therapy is well placed. For example, several gene therapy products for the treatment of cancer have demonstrated safety, and have begun to demonstrate efficacy, in clinical trials. In addition, researchers in France recently reported that infants suffering from Severe Combined Immunodeficiency Disease (SCID) have had their immune systems restored by gene therapy. And last year, American researchers described preliminary data that could lead to a gene-based cure for the debilitating blood disease, hemophilia.

Biotechnology companies rely on the promise of future revenues to support their heavy investment in the research, development, and clinical investigation of gene therapy products. The first biologics license application (BLA) for a gene therapy product may soon be submitted to FDA, but many more products are still in the early stages of clinical testing. Researchers continue to explore different indications, routes of administration, dosing regimes, patient populations, combination therapies, and novel vectors. In the meantime, gene therapy generates no revenue. The industry must finance its research, development, and testing based on the expectation of future revenue from products that eventually gain marketing approval.

The recent NIH proposal presents a grave risk to the biotechnology industry. NIH proposes to release raw adverse event data and preliminary effectiveness data obtained by product sponsors in the course of their clinical trials. In many instances, these data constitute confidential commercial information or trade secrets. Disclosure of such confidential information would jeopardize a company's future revenue, and thus undermine its ability to recoup the investment made in research and development. If NIH established a system whereby the confidential commercial information and trade secrets

of the biotechnology industry were released to the public, it would deter investors from providing the capital that allows companies to survive financially until their products can gain marketing approval.

As the NIH itself recognized in a brief filed on January 25, 2001, in a Freedom of Information Act case, "pharmaceutical and biomedical companies – and even nonprofit institutions – are generally willing to take the considerable economic risk required to develop products whose merit is not yet proven only if they can be guaranteed that confidential business information associated with these products will not be released." This is particularly true in the biotechnology sector, where many companies have no commercial products and no cash revenue. As NIH suggests in this brief, a system whereby proprietary information was routinely disclosed to the public would put an end to research and development.

I. BACKGROUND

In this section, we discuss in detail FDA's regulation of gene therapy and NIH oversight of gene therapy trials. We show that FDA is a regulatory agency with clear statutory responsibility to regulate gene therapy clinical trials. NIH, by contrast, is a research agency, charged by Congress with conducting and supporting biomedical research. The fundamental distinction between the missions of these two federal agencies, and the twenty-five-year history of the expanding NIH Guidelines, form the context for our specific comments on the recent proposal (at pages 18-39).

A. FDA Regulation of Gene Therapy

Primary responsibility for the regulation of new medical products, including their clinical testing, rests with the Food and Drug Administration. FDA derives this authority from two statutes: the Federal Food, Drug, and Cosmetic Act (FD&C Act), which provides a basic framework for regulation of drugs, and the Biologics Act of 1902, now codified as part of the Public Health Service Act, which gives federal officials authority over "biological products" including "any virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, or analogous product."

Some gene therapy products (for instance, viral vectors containing genetic material to be transferred) fall within the definition of biological products and are subject to the licensing provisions of the Public Health Service Act (as well as to some of the provisions – such as the "investigational new drug" provisions – of the FD&C Act). Other gene therapy products (such as chemically synthesized products intended to alter a specific genetic sequence in human somatic cells after systemic administration) are drugs within the meaning of section 201(g)(1) of the FD&C Act. Thus FDA is the federal agency charged by statute with regulating new products derived from recombinant DNA technology. FDA has stated unambiguously that "all gene therapy products are regulated by the FDA." Generally speaking, this requires an applicant for marketing approval to demonstrate, through carefully controlled clinical trials, that the product is safe and effective, or in the case of a biologic, safe, pure, and potent.

Any entity wishing to administer an investigational drug product (including a biologic) to humans must submit an investigational new drug application (IND) to FDA. An IND must contain sufficient pharmacological and toxicological data to show that it would be reasonably safe to conduct clinical trials in humans. It must also detail the product's chemical composition, structural formula, proposed

dosage form, and proposed route of administration; the investigative plan and proposed clinical trial protocol; any prior human experience (including foreign data); and any prior withdrawals from investigation or marketing. If FDA is satisfied that the preclinical data do not demonstrate an unacceptable safety risk to humans, the sponsor may begin clinical studies in humans.

FDA also requires that the sponsor secure approval of the clinical trial protocol by an Institutional Review Board (IRB). FDA regulations specify the criteria with which proposed research is to be judged by the IRB. These include: minimization of risk to the subjects, reasonable risks in relation to anticipated benefits, equitable selection of subjects, assurance of informed consent, adequate provisions for monitoring data, provisions for protecting patient privacy, and assurances that decisions to participate in research will not be coerced.

Safety Reports. During any trial, the sponsor must notify FDA and all participating investigators in a written safety report of: (1) any adverse experience associated with the use of the drug that is both serious and unexpected, and (2) any finding from tests in laboratory animals that suggests a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity. A "serious" adverse experience is one that results in death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect. Other important medical events may be considered "serious" if they jeopardize the subject and require medical or surgical intervention to prevent one of these outcomes. An adverse experience is "unexpected" when its specificity or severity is not consistent with the current investigator brochure. Alternatively, it is unexpected if its specificity or severity is not consistent with the risk information described in the general investigational plan or elsewhere in the IND. "Associated with the use of the drug" means there is a reasonable possibility that the experience may have been caused by the drug.

The safety report must be made no later than fifteen calendar days after the sponsor's initial receipt of the information. In the report, the sponsor must identify all previously-filed safety reports that concern similar adverse experiences, and analyze the significance of the new adverse experience in light of the previous reports. A telephone or facsimile report is required, in addition to a written report, if there has been an unexpected fatal or life-threatening experience associated with the use of the product. A "life-threatening" adverse experience is one that places the patient or subject at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death. The telephone/fax report must be transmitted no later than seven calendar days after the sponsor's initial receipt of the information.

A sponsor is also obligated to investigate any and all safety information received by it. If the results of follow-up investigation indicate that an adverse experience not initially determined to be reportable is, in fact, reportable, the sponsor has fifteen days to report the experience in a written safety report.

Annual reports. Within 60 days of the anniversary of the date that the IND went into effect, the sponsor must submit an annual report that includes the status and progress of each ongoing study governed by that IND, as well as a general summary of information obtained during all associated clinical and nonclinical investigations in the preceding year. The annual report must include a narrative

or tabular summary showing the most frequent and most serious adverse experiences by body system; a summary of all IND safety reports submitted during the previous year; a list of subjects who died during participation in the investigation (and the cause of death); a list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be related to the product; and a summary of significant foreign marketing developments such as withdrawal or suspension from marketing in any country.

B. NIH "Regulation" of Gene Therapy

1. Creation of the National Institutes of Health

The NIH was created by federal statute. Pursuant to that statute, NIH, acting through its Director, is charged with carrying out the purposes of section 241 of title 42: conducting, encouraging, cooperating with, and rendering assistance to other appropriate public authorities, scientific institutions, and scientists in the conduct of research, investigations, experiments, demonstrations, and studies relating to the causes, diagnosis, treatment, control, and prevention of physical and mental diseases and impairments of man. NIH is, thus, by statute a research institute, charged with conducting and supporting scientific research.

The history of NIH confirms its role as a research institute. NIH traces its roots to a 1798 statute creating a marine hospital service for merchant seamen. In 1887, a bacteriological laboratory known as the Laboratory of Hygiene was created as part of the Marine Hospital Service to research cholera and other infectious diseases. This laboratory slowly evolved into what is now the National Institutes of Health. For instance, in 1912 Congress renamed the "Public Health and Marine Hospital Service" as the "Public Health Service," instructing it to "study and investigate the diseases of man." The "National Institute of Health" was created within the Public Health Service in 1930 to conduct study, investigation, and research regarding the diseases of man. In the Public Health Service Act of 1944, Congress consolidated and revised prior legislation relating to the Public Health Service, and created the framework that still exists today. Dozens of legislative enactments over the century culminated in a 1985 bill that officially established the modern NIH, the "principal medical research arm of the Federal Government."

2. The NIH Guidelines

With the discovery of recombinant DNA technology, NIH's activities expanded beyond conducting and supporting biomedical research. At the behest of the scientific community – not Congress – NIH began to "review" and "approve" proposed rDNA experiments.

In the early 1970s, scientists announced that they had developed a method to combine genes – deoxyribonucleic acid (DNA) molecules – from two different species to form new "recombinant DNA" biological entities. Concerned about the potential impact of this new scientific capability, scientists called for a moratorium on recombinant DNA experiments pending public review of the risks. Following the establishment of a Recombinant DNA Advisory Committee at NIH in 1974, a scientific meeting at the Asilomar Conference Center in California in February 1975, and a public hearing conducted by the

National Institutes of Health in February 1976, NIH published the Recombinant DNA Guidelines in July 1976 to govern all recombinant DNA research conducted with NIH funds. Human trials were a decade away, and the 1976 Guidelines established "carefully controlled conditions for the conduct of experiments involving the production of [recombinant DNA] molecules and their insertion into organisms such as bacteria."

In 1984 NIH issued the first version of the current NIH Guidelines. These Guidelines – like the current ones – applied to experiments conducted with NIH funding and to experiments conducted at institutions receiving NIH funding for other gene therapy research. Based on the premise that recombinant DNA research in humans posed unique ethical issues, the Guidelines required submission to NIH of information related to proposed human gene therapy experiments, public review of that information by the RAC, and approval of the experiment by the RAC. Although RAC meetings were open to the public, the Guidelines permitted institutions to designate portions of their submissions as trade secret, privileged, or confidential commercial or financial information. In 1986 NIH began requiring more detailed information about proposed human experiments, and in 1990 it added provisions requiring adverse event reports and biannual summary reports.

Human gene therapy has progressed from an initial human experiment in 1984 to the development and clinical investigation of hundreds of potentially therapeutic products by commercial sponsors in 2001. Until October 1997, any clinical investigation of these products required approval by an IRB, authorization by FDA after submission and review of an IND, and approval by the NIH RAC. In 1996, NIH itself proposed to eliminate RAC review and approval of gene therapy clinical research, on the theory that IRB and FDA review was sufficient. When this became controversial, NIH issued a compromise that left the RAC review process intact while technically eliminating the requirement of RAC "approval." The October 1997 Guidelines established the process that governs submissions to NIH today.

Under the October 1997 Guidelines, as modified slightly in October 2000 and January 2001, NIH requires the submission of detailed information about proposed and ongoing gene therapy trials in humans, and provides for public review of much of this information. Specifically, an investigator must submit the clinical protocol governing the proposed experiment, informed consent documents, and answers to a series of questions designed to flesh out the research design. These questions address, among other things: the structure and characteristics of the biological system to be used, results of preclinical studies including risk/benefit studies, a description of the delivery system, description of measures to be taken to reverse or control adverse events, results of any similar protocol conducted in nonhuman primates and other animals, and clinical procedures including the endpoints of the study and the nature of patient monitoring.

Under the NIH Guidelines, an investigator who has received approval from FDA to initiate a human gene transfer protocol must report any "serious" adverse event "immediately" to the local Institutional Review Board, Institutional Biosafety Committee, Office for Human Research

Protections (if applicable), and the NIH OBA. The investigator must follow up with a written submission. The Guidelines do not define "serious adverse event" but NIH takes the position that the phrase includes events that are expected or unexpected, and events that are related or unrelated to the gene therapy. Investigators must also submit annual reports. The Guidelines do not address the content or the timing of annual reports. The NIH Guidelines state that a form for annual reporting is available from NIH OBA, but in fact the OBA no longer distributes a standardized form. Annual reports tend, therefore, to vary in both content and format. Sponsors, who usually assume responsibility for submitting both adverse event reports and annual reports, usually submit summary safety data in their annual reports, often in tabular form.

On November 22, 1999, NIH proposed modifications to the adverse event report provisions of the Guidelines. Comments were due in December, and the proposal was discussed at a RAC meeting in the same month. In its statement about the proposal, BIO explained that adverse event reports during clinical trials of an investigational product contain trade secrets and confidential commercial information. BIO explained why NIH may not release this information to the public. BIO also argued that serious adverse event reporting to NIH and to FDA should be harmonized, to eliminate confusion and to reduce the burden on investigators and sponsors. The timing of the reports should be identical, and the agencies should use the same definition of "serious adverse event." In the eleven months that followed, NIH, FDA, investigators, sponsors, Members of Congress, patient groups, and others engaged in what NIH calls an "in depth, year-long, public debate and discussion" about the role of NIH in federal "oversight" of gene therapy trials. The current proposal is the result of that year-long discussion.

3. **The Evolution of the NIH Guidelines**

When the RAC was established in 1974, it was envisioned as a scientific advisory body that would consider and respond to concerns about potential biohazards associated with recombinant DNA research. The NIH Guidelines adopted in 1976 consisted, for the most part, of biological and physical containment procedures. They were designed to ensure that the new research posed no threat to those engaged in the research, to the general public, or to the environment.

Over the last two decades, however, the NIH Guidelines have mushroomed into an elaborate set of rules that apply to nearly every private company engaged in the development of commercial gene therapy products. Most institutions suitable for hosting clinical trials of gene therapy receive at least some federal funding for recombinant DNA research. Accordingly, as a practical matter, most sponsors believe they have no choice but to comply with the NIH Guidelines. The Guidelines thus function more like regulations than agency policy statements. Moreover, the requirements set forth in the NIH Guidelines are the sort of legal obligations that would ordinarily be imposed by a regulatory agency pursuant to an explicit statutory grant of authority, and pursuant to the rulemaking procedures of the Administrative Procedure Act. Such regulations would be subject to the Paperwork Reduction Act, the Regulatory Flexibility Act, and various presidential executive orders.

NIH has typically followed a truncated form of notice-and-comment when modifying its Guidelines. However, the Agency has never acknowledged that the APA might apply to the Guidelines, and it has not purported to adopt the Guidelines in conformity with the several other statutes and executive orders that apply to "regulations." Indeed, in 1976 NIH explicitly chose to proceed through guidelines rather than regulations, in order to retain some "flexibility" and "administrative efficiency." However the "Guidelines" of 2001 look nothing like the "Guidelines" of 1976. The 1976 Guidelines were a simple set of physical and biological containment practices prescribed for the creation of and experimentation with recombinant DNA molecules. The NIH policy in 2001 is embodied in an entirely different document – one which imposes mandatory substantive obligations and which establishes an elaborate regulatory framework. As a result of the way in which this framework has evolved, institutions, investigators, and sponsors today face considerable uncertainty about their legal rights and obligations when conducting gene therapy research, and about the consequences of their failure to comply with every expressed preference of the NIH. Uncertainties about the precise nature and effect of the Guidelines will only exacerbate the problems highlighted in part II of our comments.

II. SPECIFIC COMMENTS ON THE NIH PROPOSAL

A. Description of the Proposal

On December 12, 2000, NIH issued a proposal to modify the adverse event report and annual report provisions of the NIH Guidelines. The proposal has four elements.

First, NIH proposes to revise its description of adverse event reports. A serious adverse event would be "any event occurring at any dose that results in any of the following outcomes: Death, a life-threatening event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability [or] incapacity, or a congenital anomaly [or] birth defect." Also, "important" medical events that might not result in death, be life-threatening, or require hospitalization, could be considered serious adverse events if "upon the basis of appropriate medical judgment, they may jeopardize the human gene transfer research subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition."

A serious adverse event that was (a) fatal or life threatening, (b) unexpected, and (c) possibly associated with the use of the gene transfer product, would need to be reported to OBA no later than seven calendar days after the sponsor's initial receipt of the information (i.e., the proposal indicates, "at the same time the event must be reported to the FDA"). Serious adverse events that were (a) unexpected and (b) possibly associated with the use of the gene transfer product, but were not fatal or life threatening, would need to be reported to OBA no later than fifteen calendar days after the initial receipt (i.e., the proposal states, "at the same time the event must be reported to the FDA"). An event would be "associated with the use of a gene transfer product" if there were a "reasonable possibility that the event may have been caused by the use of that product." It would be "unexpected" if its specificity or severity were not "consistent" with the "risk information currently available in the protocol."

Follow-up information relevant to a serious adverse event would need to be reported within fifteen days of the receipt of the information. Any finding from tests in laboratory animals that suggested a "significant risk for human research participants" including reports of mutagenicity, teratogenicity, or carcinogenicity, would need to be reported no later than fifteen days after the sponsor's initial receipt of the information (i.e., the proposal states, at the same time the event must be reported to FDA).

NIH also proposes to authorize explicitly a practice that has become commonplace under the NIH Guidelines: It would permit sponsors to assume responsibility for adverse event reporting on behalf of investigators.

Second, NIH proposes to amend the provision on annual reports. An annual report to NIH would be roughly the same as an annual report to FDA. The report would contain clinical trial information, a progress report, data analysis, and a copy of the updated clinical protocol. The data analysis would include analysis of the safety data available, including a summary of serious adverse events that were expected or considered to have causes not associated with the use of the gene transfer product. The annual report would also include: "a brief description of any information obtained pertinent to an understanding of the gene transfer product's actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability." Annual reports would be due to OBA within sixty days of the one year anniversary of the date on which the clinical trial was initiated, and of each subsequent anniversary, until completion of the clinical trial.

Third, NIH proposes that absent extraordinary circumstances, "information submitted in accordance with Appendix M-I-C" would be considered public. NIH states that "safety reports submitted in accordance with Appendix M-I-C will *not* be considered to constitute or contain *any* trade secret or commercial or financial information that is privileged or confidential as defined under the Freedom of Information Act, 5 U.S.C. 552." NIH's intent with regard to the confidentiality of annual reports, on the other hand, is not clear. The just-quoted statements appear in proposed M-I-C-4-a (serious adverse event reports) and not in M-I-C-3 (annual reports). However, the phrase "information submitted in accordance with Appendix M-I-C" would sweep within its scope both adverse event reports and annual reports.

Fourth, NIH proposes the creation of a standing working group of the RAC to review adverse event reports and annual reports. The "NIH Gene Transfer Safety Assessment Board" would be composed of members appointed by the NIH Director. Only two would need to be members of the RAC. No other limitations would be placed on the membership of the group, although NIH indicates the group would be composed of "government and non-governmental experts in relevant clinical specialties" and "would include liaison representation from the FDA." The working group would be charged with four tasks. It would review all serious adverse event reports, annual reports, and safety information submitted to OBA. It would identify significant trends and events in those documents. It would develop information to enhance the development, design, and conduct of human gene transfer clinical trials. And it would report aggregated trend data to the RAC "to enhance review of new protocols" and "to enhance public awareness of the safety of human gene transfer research studies as well as the informed decision-making of potential trial participants."

B. **The Proposed Guidelines Would Publicly Disclose Trade Secrets and Confidential Information, in Violation of the Trade Secrets Act and the Takings Clause.**

Serious adverse event reports and annual reports during the IND phase of a new biologic or drug have long been recognized as "confidential commercial information" and/or "trade secrets" within the meaning of Exemption 4 of the Freedom of Information Act (FOI Act). As such, they also fall within the scope of the Federal Trade Secrets Act, and their disclosure to the public would violate federal criminal law. Their disclosure to the public could also constitute a "taking" in violation of the Fifth Amendment to the United States Constitution.

1. **Serious Adverse Event Reports and Annual Reports are Trade Secrets and/or Confidential Commercial Information Within Exemption 4 of the FOI Act.**

Exemption 4 of the FOI Act provides that "trade secrets and commercial or financial information obtained from a person and privileged or confidential" are exempt from disclosure. The courts use different tests to determine whether information is within Exemption 4, depending on whether the information is voluntarily submitted to the government.

As explained above (page 16), compliance with the NIH Guidelines is effectively "mandatory" for FOI purposes. Most institutions suitable for hosting clinical trials of gene therapy receive at least some federal funding for recombinant DNA research, and most sponsors believe they have no choice but to comply with the NIH Guidelines. In addition, as the Department of Justice reports in its manual on the FOI Act, "'submission that are required to realize the benefits of a voluntary program are to be considered mandatory.'"

Information required to be submitted to the government is protected by Exemption 4 if its disclosure would cause substantial competitive harm to the submitter. Disclosure of serious adverse event reports and annual reports prior to FDA approval could cause substantial competitive harm to a sponsor. For example, some experiences during a clinical trial that would be classified as "adverse events" might in fact suggest a new indication for research and development. Disclosure of such an event could cost the company the opportunity to patent its product for the new indication in question. To give another example, the rate of adverse events can indicate the number of patients currently enrolled in clinical trials of a product. From this information, a competitor can determine the stage and the pace of a company's product development.

Similarly, the information in an annual report would be of tremendous value to a competitor in the early stages of developing a competing product. A competitor could combine dose response information, preliminary effectiveness reports, and preclinical study results (submitted to NIH before the trial commences) to design a study specifically to demonstrate the superiority of its competing drug. (Ordinarily, a competitor would not have enough information to tailor its investigational plan in this manner.) Dose response information could tell the competitor which dose levels work and which do not. Dose response information combined with adverse event reports might show the maximum tolerable dose. The number of patients completing the trial, and the number of

patients that have dropped out, could indicate if there was a problem with the study design, protocol requirements, dose, testing, or logistics. The previous year's clinical and non-clinical investigations could give a competitor an inside view of a company's development plan and perhaps even insight as to the specific animal models being developed for preclinical work. Some of this information could suggest agreements a company has with FDA. Protocol amendments to expand patient cohorts, or the addition of preclinical studies, could tell a competitor whether a company has made process changes. In short, disclosure of the information in an adverse event report and an annual report could allow a competitor to duplicate a company's work without the same expenditure of time and money, or even allow it to avoid expensive and time-consuming research altogether. The reports are therefore within Exemption 4.

Even if the submission of adverse event reports and annual reports to NIH were held to be "voluntary," they would fall within the scope of Exemption 4. Material submitted voluntarily to an agency is confidential and within Exemption 4 if it is "of a kind that would customarily not be released to the public by the person from whom it was obtained." For the reasons discussed on the preceding pages, the contents of adverse event reports and annual reports would not customarily be released to the public by a pharmaceutical or biotechnology company.

The courts agree that, prior to approval of a product, adverse event reports and annual reports fall within the scope of the confidential commercial information exemption to the FOI Act. In August 1999 the United States Court of Appeals for the D.C. Circuit found four abandoned INDs – which contained FDA adverse event reports and annual reports – within Exemption 4. This ruling confirmed the D.C. Circuit's long-held view that disclosure of any information that would help a pharmaceutical or biotechnology company's competitors bring a competing product to market more quickly and less expensively is the essence of competitive harm. This judicial doctrine dates at least to 1983, when the D.C. Circuit concluded that manufacturers "have a commercial interest in" – and the desire to keep confidential – the "health and safety experience of their products." The court then held that manufacturers of intraocular lenses had adequately demonstrated that safety information submitted to FDA, if released, could be used by competitors, and thus that summary judgment under Exemption 4 was supportable with respect to the vast majority of the requested records.

In the December 2000 *Federal Register* notice, NIH offers an unlawful interpretation of Exemption 4. It dismisses Exemption 4 in one pronouncement: "The concept that reports of adverse events should be considered from a commercial standpoint as confidential, however, is contrary to NIH's commitment to public access to information about the safety of human gene transfer research." However, the public's asserted interest in information about the safety of human gene transfer research does not control the legal question under Exemption 4. The FOI Act was written to further the public's interest in information "about the workings of the Government." The FOI exemptions reflect Congress's determination that certain "legitimate governmental and private interests" outweigh that public interest. The "collateral benefits of disclosure" (e.g., furthering the public's interest in information about new medical

technology) are not part of the legal inquiry under Exemption 4. In other words, as the D.C. Circuit wrote in 1999, "Congress has already determined the relevant public interest." Thus, NIH's "commitment" to providing the public with information about gene therapy trials must give way to the congressional protection granted to trade secrets and confidential commercial information.

2. **Public Disclosure of Serious Adverse Event Reports and Annual Reports Would Violate the Trade Secrets Act.**

Federal criminal law prohibits NIH, as well as its officials, employees, and RAC members, from disseminating material within Exemption 4 of the FOI Act. This included material in adverse event reports and annual reports.

The Trade Secrets Act prohibits any federal employee from disclosing any "trade secrets, processes, operations, style of work, or apparatus." The Supreme Court has characterized it as "a general criminal statute that provides a penalty for any employee of the United States Government who discloses, in any manner not authorized by law, any trade-secret information that is revealed to him during the course of his official duties." The Department of Justice (DOJ) describes the Trade Secrets Act as "an extraordinarily broadly worded criminal statute" which "prohibits the disclosure of much more than simply 'trade secret' information and instead prohibits the unauthorized disclosure of all data protected by Exemption 4." FDA similarly describes the Trade Secrets Act as a "general Federal prohibition against disclosure of trade secret information" under which "[d]isclosure of information . . . constitutes a criminal offense."

NIH appears to recognize that the Trade Secrets Act applies to material submitted under the NIH Guidelines. Section IV-D-5-a of the Guidelines states that: "it is a criminal offense for an officer or employee of the U.S. or any Federal department or agency to publish, divulge, disclose, or make known 'in any manner or to any extent not authorized by law any information coming to him in the course of his employment or official duties or by reason of any examination or investigation made by, or return, report or record made to or filed with, such department or agency or officer or employee thereof, which information concerns or relates to the trade secrets, (or) processes . . . of any person, firm, partnership, corporation, or association.'" Lest there be uncertainty about the applicability of this criminal provision to RAC members, NIH adds that "Members of RAC are 'special Government employees.'" Despite these statements in the NIH Guidelines, however, to our knowledge NIH has not analyzed the applicability of the Act to submissions under Appendix M.

The Trade Secrets Act applies not only to individual acts of disclosure, but also to agency decisions and regulations that provide for disclosure. As the Supreme Court held in *Ruckelshaus* v. *Monsanto Co.*, the statute is "more than an 'anti-leak' statute aimed at deterring Government employees from profiting by information they receive in their official capacities." Thus, in *Chrysler Corp.* v. *Brown*, the Supreme Court held that the Act applies to "formal" agency actions, and that the presence of agency regulations authorizing disclosure would not make that disclosure

"authorized by law" within the meaning of the statute. Indeed, the Department of Justice says, the "practical effect" of the Trade Secrets Act is to limit an agency's ability to make a discretionary release of otherwise exempt material, because to do so in violation of the Trade Secrets Act is not only a criminal offense, it also constitutes "'a serious abuse of agency discretion' redressable through a reverse FOIA suit."

Under the Trade Secrets Act, therefore, no NIH employee and no RAC member may disclose, in any forum or at any time, during or after government service, the trade secrets and confidential commercial information contained in any submission under the NIH Guidelines. This includes, but is not limited to, information included in adverse event reports and annual reports by sponsors of gene therapy trials. Public dissemination by NIH of the content of these reports would violate federal criminal law.

3. **Public Disclosure of Adverse Event Reports and Annual Reports Would Violate the Takings Clause of United States Constitution.**

Public dissemination of adverse event reports and annual reports would also constitute a "taking" of property for public use without just compensation, in violation of the Fifth Amendment to the United States Constitution.

It is well established that trade secrets and confidential commercial information are "property" protected by the Fifth Amendment to the United States Constitution. With respect to such property, "the right to exclude others is central to the very definition of the property interest. In short, the essence of ownership of a trade secret or confidential commercial information is the right to exclude others. Once secrecy has been lost, the property has been irrevocably destroyed.

Government action constitutes a *per se* taking if it deprives the property owner of all economically beneficial use of his property, or if it constitutes an appropriation of one or more of the property owner's fundamental ownership rights in the property (including the right to exclude others from making use of the property). Disclosure of trade secrets and confidential commercial information compiled during the testing of an investigational new drug or biologic – including adverse event reports and annual reports – would do both. As explained above (pages 23-24), by disclosing information that would allow a company's competitor to duplicate its research without the same expenditure of time and money or to avoid that research altogether, NIH would strip the company of its ability to use that information profitably in a commercial setting.

Even if public disclosure of adverse event reports and annual reports were not a *per se* taking, it would be a compensable "regulatory taking." Although there is no precise formula for determining when a regulatory taking has occurred, the Supreme Court examines "the character of the governmental action, its economic impact, and its interference with reasonable investment-backed expectations." BIO members have invested millions of dollars in the research and development of gene therapy products. As explained above (pages 23-24), disclosure of the trade secrets and confidential commercial information contained in adverse event reports and annual reports would have a devastating

economic impact on the sponsors of such products by compromising their future revenue and thus their ability to recoup their investments in research and development. These investments were made with the understanding and expectation that FDA and NIH would continue to comply with the federal Trade Secrets Act and would continue to withhold from public disclosure data and information within Exemption 4 of the FOI Act. In short, BIO members have – and continue to have – reasonable investment-backed expectations in the continued legal protection of their trade secrets and commercial information. The reasonableness of these expectations is underscored by the Department of Justice's position that the Trade Secrets Act extends to everything within Exemption 4 of the FOI Act, the court cases confirming that adverse event reports and annual reports fall within Exemption 4, and the position recently taken by NIH in *Public Citizen Health Research Group* v. *NIH*.

C. **Review and Analysis of Adverse Event Reports and Annual Reports by a Working Group Would Adequately Further the RAC's Goals, While Protecting Trade Secrets and Confidential Commercial Information.**

Disclosure of raw adverse event data to the public would not further the RAC's broad educational mission. In addition, it would be contrary to the public interest. A working group – but not the working group that NIH proposes – should review raw adverse event reports and provide a synthesis of those reports to the RAC and the public on a quarterly basis.

1. **Disclosure of Raw Adverse Event Reports to the Public is Not Necessary and Would Be Contrary to the Public Interest.**

NIH describes its mission as that of gathering information about the safety of gene therapy trials, for several purposes: to facilitate public understanding of the technology, to foster discussion about the risks and benefits of gene therapy, and to foster discussion about the social and ethical issues raised by gene therapy. However, public review of individual adverse event reports and annual reports is unnecessary for RAC to fulfill this broad educational function. Discussion of the nature of gene therapy technology, as well as its risks and benefits, can be explored by the RAC without reference to any specific company or its clinical trials. The social and ethical questions relating to non-germ-cell gene therapy have been discussed in public for twenty-five years. The RAC's broad educational mission can be achieved without disclosure of individual raw adverse event reports, preliminary dose response data, or other preliminary effectiveness information.

NIH proposes a working group that would review, aggregate, and analyze adverse event reports and annual reports. This working group should be the mechanism by which NIH accomplishes its stated objective. Adverse event reports and annual reports (without preliminary effectiveness information) should be provided, on a confidential basis, to the working group. The group should perform the tasks that NIH has set forth: (1) review of those reports, (2) identification of significant trends and even significant individual events in the documents, (3) development of information that might enhance the development, design, and conduct of gene therapy trials, and (4) report of aggregated trend data to the RAC and to the public. This would accomplish NIH's stated objectives.

Moreover, raw adverse event data can be confusing and misleading. Raw adverse event reports can be misinterpreted. For example, Representative Waxman's office recently drew dangerously incorrect conclusions about the adverse events reported in a lung cancer gene therapy trial. In a letter to the Acting Director of NIH in February 2000, Representative Waxman explained that his staff had reviewed adverse event reports submitted to NIH from gene therapy trials, and suggested that gene therapy was responsible for the death of 38 out of 48 patients in a lung cancer gene therapy trial. In response to the Waxman letter, at a recent RAC meeting, a scientist from the National Cancer Institute presented information demonstrating that most of the 38 deaths were due to the progression of underlying disease. A further review of data led to the conclusion that none of the 38 deaths were related to the gene therapy treatment. In short, Representative Waxman's staff drew an erroneous conclusion from raw adverse event data, because it lacked all of the necessary information. The erroneous conclusion drawn by Representative Waxman's staff was disseminated widely by the press. Erroneous reports like this could have a devastating impact on recruitment for clinical trials, and on the industry's ability to attract investors. Ultimately, misinterpretation of raw adverse event data could interfere with the ability of the industry to bring important new therapeutic products to market.

Disclosure of individual raw adverse event reports can also jeopardize ongoing clinical trials. Some sponsors report adverse events with the blind maintained. Disclosure of these adverse events could unnecessarily alarm trial participants and skew the study results. (For instance, many adverse events in gene therapy trials result from disease progression.) For similar reasons, disclosure of a blinded serious adverse event could put a company in the untenable position of choosing between continuing its trial or reassuring its investors. For instance, suppose a patient in a blinded study of a treatment for end-stage cancer died and the adverse event were reported (on a blind basis) to the RAC. Suppose the information were made publicly available, and the media reported the death. If the report were blind, the media and the public would have no information about the context of the adverse event – for example, whether the patient was on placebo or study drug, or whether the patient died as a consequence of advanced disease. Investors could demand clarification and explanation. A start-up venture with no marketed products could face the untenable choice between breaking the blind to respond to questions (which would jeopardize the trial results and delay clinical development), and retaining the blind and risking sell-off of its stock by nervous, partially informed, or misinformed investors (which would jeopardize its entire clinical development program).

In sum, disclosure of raw adverse event reports would do little to inform the public and could have serious adverse impacts on the research and development of new gene therapy products.

2. **The Working Group Proposed by NIH Would Not Adequately Protect Trade Secrets and Confidential Commercial Information.**

Over a year ago, BIO urged NIH to create a working group, composed of FDA and NIH employees, which would review adverse event reports on a confidential basis and present summary reports on a quarterly basis to

the RAC. While NIH has proposed a working group to review adverse event reports and annual reports, the NIH proposal falls short in three respects.

First, the working group should be composed solely of full time government employees, who are bound by the Trade Secrets Act. NIH should explore the value of locating the working group within FDA, and staffing it exclusively with FDA scientists who have experience with raw adverse event reports and access to the IND, which may provide necessary contextual information. In the alternative, members could be selected from FDA, the United States Department of Agriculture, the Centers for Disease Control, and the National Institutes of Health. At a minimum, NIH should make explicit the fact that non-government employees who join the working group are "special government employees" subject to the Trade Secrets Act.

Second, NIH must explicitly state that adverse event reports and annual reports submitted to NIH will be deemed within the Trade Secrets Act and will be kept confidential by NIH, its officials, its staff, the RAC, and the working group.

Third, NIH should institute a conflicts check and a mandatory recusal provision to ensure that a company's trade secrets and confidential commercial information are not seen by its competitors or by industry consultants. In light of the revolving door between government, academia, and industry, NIH should supplement the Trade Secrets Act with these safeguards.

D. **NIH Should Permit Investigators to Submit the Same Information in Adverse Event Reports that Sponsors Submit to FDA in IND Safety Reports.**

In its current proposal NIH has taken important first steps towards harmonizing reporting under the NIH Guidelines with reporting under FDA regulations. The proposed definition of "serious adverse event" is essentially consistent with the FDA definition of "serious adverse drug experience." To make the provisions entirely consistent, NIH should state that a seven day report must be filed if the event was "associated" with the use of the product (not "possibly associated" with the use of the product). Under both FDA regulations and the NIH proposal, an event would be "associated with the use of the product" if there were a "reasonable possibility" that the event may have been caused by the product. NIH should therefore eliminate the initial and superfluous "possibly." In addition, under the proposal serious adverse event reports would be filed with NIH at the same time as they are filed with FDA. This should eliminate the confusion caused by the different reporting systems, and it should reduce the burden of complying with different deadlines. Ultimately this revision to the NIH Guidelines should help to ensure that adverse event reporting to NIH is complete and accurate.

NIH proposes, however, to require the submission of information in adverse event reports that FDA does not require in IND safety reports. Among other things, NIH proposes to require, in each adverse event report: the gene delivery method, the vector type, the vector subtype, the dosing schedule, and the route of administration. Much of this information is proprietary and protected by the Trade Secrets Act. Moreover, sponsors do not submit this information to FDA or Form 3500A (the "MedWatch" form). NIH should permit investigators to submit

the same information to NIH that sponsors submit to FDA. Completion of significantly different forms will be confusing and burdensome for both investigators and sponsors.

E. **NIH Should Require the Submission of Safety Data Only, in Annual Reports, and It Should Harmonize the Annual Reporting Deadline with FDA Regulations.**

The proposed annual report provisions should be substantially revised.

First, annual reports should contain only safety information. The FDA IND annual report regulation is not an appropriate model. The proposed NIH Guidelines would require reporting of information unrelated to safety: "a brief description of any information obtained pertinent to an understanding of the gene transfer product's actions, including, for example, information about dose-response, information from controlled trials, and information about bioavailability." This is preliminary effectiveness information. FDA requires such information under 21 C.F.R. § 312.33(b)(5) because an annual report to FDA is a "progress report" about a clinical trial, and a preliminary analysis of the safety *and effectiveness* of the investigational product in question. By way of contrast, NIH states in its proposal that its goal is to gather information about *safety* and to enable public discussion by the RAC of important developments in the *safety* of human gene therapy. In other words, NIH professes no interest in effectiveness information. Moreover, as explained above (see pages 23-24), preliminary effectiveness information is highly confidential. Proposed M-I-C-3(b)(5) should therefore be eliminated.

Second, annual reports should be submitted to NIH when they are submitted to FDA. NIH proposes to require that an investigator file an annual report within 60 days "of the one year anniversary of the date on which the clinical trial was initiated and of each subsequent anniversary until the trial is completed." At FDA, the sponsor must file its annual report "within 60 days of the anniversary date that the IND went into effect." If multiple trials are conducted under one IND – as is usually the case – they will be folded into one annual report at FDA. NIH would apparently require a separate report for each trial. This will be a cumbersome and confusing process for investigators, and for sponsors (who may have trials that NIH does not "regulate"). NIH characterizes the annual report proposal as having been harmonized with FDA regulations. Accordingly, we assume that the use of the clinical trial start date, rather than the IND effective date, was an oversight. NIH should revise the annual report provision to require annual reports 60 days after the anniversary of the date that the governing IND went into effect.

Third, NIH should state that it will respect the confidential status of annual reports. As explained above (pages 22-26), annual reports contain trade secrets and confidential commercial information within the scope of Exemption 4 of the Freedom of Information Act. Their disclosure to the public would be a violation of federal criminal law.

III. CONCLUSION

Human gene therapy has progressed from the first human experiment in 1984 to the development and clinical investigation of commercial products by biotechnology and pharmaceutical companies. The first biologics license application (BLA) for a gene therapy product may soon be submitted to FDA. As explained in these comments, the

time has come for NIH to reconsider the premises of the NIH Guidelines, and their effect on the developing industry. The RAC has an important role to play in facilitating public discussion of broad social and ethical issues relating to gene therapy. However, it is neither wise nor lawful for NIH to disseminate to the public raw safety information and preliminary effectiveness information pertaining to investigational drug products.

Respectfully submitted,

BIOTECHNOLOGY INDUSTRY ORGANIZATION

by Carl B. Feldbaum, President